Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled "Therapeutic methods and compositions for the treatment of impaired interpersonal and behavioral disorders".

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number PCT/EP0006259

on June 22, 2000,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/140563 (Application Number)	June 23, 1999 (Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Martin M. Zoltick, Reg. No. 35,745; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; and Paul E. Rauch, Reg. No. 38,591; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true: and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Tony MARCEL
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Signature of Inventor

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Signature of Inventor

Date

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NAME OF FIFTH JOINT INVENTOR

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Citizen of:

Post Office Address:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re-application of
Marcel et al.

Group art Unit : 1647

Serial N° : 10/024,535

Examiner : Wegert, Sandra L.

Filed : 12/21/2001

For : Therapeutic methods and compositions for the treatment of impaired personal and behavioural disorders

DECLARATION UNDER RULE 37 C.F.R. § 1.132

Hon. Commissioner of Patents and Trademarks
WASHINGTON D.C. 20231
Sir :

I, Marie-Noëlle RENONCET-UNGEHEUER, residing at 12 rue de Bénodet, 78310 Maurepas (France) ;
Declare and say :

I am citizen of France.

I am MD, graduated from the University of Rennes I (France), and PhD, graduated from the University of Paris VI (France).

Currently, I have the position of Medical Investigator at the Medical Center of Institut Pasteur.

The use of animals, such as rodents, to model human physical and mental disorders has long been an integral part of medical and scientific research and it is expected that rodents will carry the main workload of animal research aimed at treating human disorders for some time to come (e.g. Dobbing, J., "Undernutrition and the developing brain. The relevance of animal models to the human problem", Bibl. Nutr. Dieta 17:35-46 (1972) ; Shaywitz, B. A. et al., "Animal models of neuropsychiatric disorders and their relevance for Tourette syndrome,", Adv. Neurol., 35:199-202 (1982) ; and Newport, D.J., "Parental depression : animal models of an adverse life event,", Am. J. Psychiatry, 19:1265-1283 (2002)). For example, complex human behavioural conditions have been successfully modelled in animals. Rodent models of psychiatric disorders such as schizophrenia, fear and anxiety, depression and alcoholism are well established and these models are being actively pursued to identify effective therapies to treat humans afflicted with these disorders (e.g. Hitzemann, R., "Animal Models of Psychiatric Disorders and their Relevance to Alcoholism" Alcohol Res Health 24:149-158 (2000) ; and Ellenbroek, B.A. "Effects of JL13, a pyridobenzoxazepine with potential atypical antipsychotic activity, in animal models for schizophrenia," J. Pharmacol Exp Ther" 298:386-391 (2001)).

The Examiner opines that the description of experiments in normal rats is not adequate written description of a genus of treatment methods that can be applied to humans. I respectfully disagree.

For instance, sexual behaviour studies in rats have had predictable and similar outcomes in humans. For example, studies of sexual disorders in male rats have shown that androgens are essential in the maintenance of nitric oxide-mediated penile erections as in human males (Aversea, A., et al., "Androgens and penile erection : evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction" Clin Endocrinol, 53:517-522 (2000)). Another example involves the treatment of male rats with the estrogen delivery system, E2CDS. This treatment resulted in a decrease in the levels of luteinizing hormone and chronic stimulation of male sexual behaviour. Human clinical trials

with E2CDS were found to decrease luteinizing hormone levels in a similar fashion to that seen in rats (Brewster, M. et al., "Brain-Targeted Delivery of Estrogens", Review in the Neurosciences 2:241-285 (1990)). Furthermore, estradiol treatment has been proven to stimulate libido in human male subjects, matching the sexual stimulation in male rats (Bancroft, J. et al., "The control of deviant sexual behaviour by drugs : behavioural changes with oestrogens and anti-androgens", British Journal of Psychiatry 125:310-315 (1974)).

All of these studies point to the rat as being a good system for modeling human sexual disorders. Given the burgeoning collection of studies showing that rodent models are satisfyingly predictive of human sexual disorders, I believe, as one skilled in the art, that the results described in the above-referenced patent application are supportive of the claimed invention. In my opinion, as one skilled in the art, I contend that there is a very reasonable basis for expecting the disclosed method of treatment to be successful in treating humans with mental disorders, especially impaired social activity linked to sexuality.

Although some animal models closely mirror the human condition, most animal models are unable to recapitulate the human disorder. Yet they have proven to be valuable (Sarkisian, M.R., "Overview of the current animal models for human seizure and epilieptic disorders" Epilepsy & Behavior : E&B 2:201-216 (2001) ; Shahbazian M et al. "Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3" Neuron 18:243-254 (2002) ; Freeze, H.H., "Human disorders in N-glycosylation and animal models" Biochim Biophys Acta 1573:388-393 (2002) ; and Maurer, M. and Gold, R. "Animal models of immune-mediated neuropathies" Curr Opin Neurol 15:617-622 (2002)). Normal animals have also been of use in advancing new therapies for human sexual disorders. A good example of this is the use of normal rodents in testing sildenafil (Viagra). Viagra modifies sexual arousal and ejaculatory mechanisms in normal rats in a similar manner to humans (Gemalmaz H. et al., "In vivo and in vitro investigation of the effects of sildenafil on rat cavernous smooth muscle" J. Urol. 165:1010-1014 (2001) ; Tsukamoto, J. et al., "Treatment of erectiledysfunction : what should we do next ?" World J. Surg., 24:1180-1182 (2000) ; Ottani A. et al., "Modulatory activity of

sildenafil on copulatory behavior of both intact and castrated male rats" Pharmacol Biochem Behav 72:717-722 (2002) ; and Ueno, N. et al. "The effect of sildenafil on electrostimulation-induced erection in the rat model" International Journal of Impotence Research 14:251-255 (2002)). The improvement over the baseline of sexual activity in normal rats, upon treatment with sildenafil, correlates well with the improved sexual activity of similarly treated human males. Thus, normal rats can serve as good models when an increase over baseline in a phenotype such as sexual behavior is sufficient to ameliorate a similar human condition.

The specification of the patent application discloses improvement of sexual behaviour, in a rodent model, by administration of the QHNPR peptide as a basis for the efficiency of the QHNPR peptide in humans. The specification clearly indicates that treatment of male rodents with this peptide improves their sexual behaviour (see Examples 3 through 7 on pages 17-21). Based on this disclosure and the art in the field of animal modelling of human disorders, in my view there is a reasonable basis to believe that treatment of humans afflicted with sexual disorders using the QHNPR peptide would be successful. As indicated above, there is sufficient evidence in the field that rats are good models for human conditions.

The Examiner has opined that there would be undue experimentation involved in reducing the claims to practice, that is, in treating a mental disorder, in particular impaired social activity linked to sexuality, in humans with the QHNPR peptide. More experimentation would ultimately be done in humans to obtain FDA approval. Nevertheless, this does not make the experimentation undue, as such testing has been performed in the art. Almost all human clinical studies have their origin in animal models and the art typically engages in pursuing human studies after evaluating the results from animal models.

The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 2nd day of June 2005

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MEDECIN DE RECHERCHE CLINIQUE

Médecin de Recherche Clinique depuis septembre 2002 au Centre Médical de l'Institut Pasteur (CMIP).
Investigateur dans des études de physiopathologie initiées par des chercheurs du campus pasteurien,
Responsable d'ICARe (Investigation Clinique et Appui à la Recherche) au CMIP.
Organisation d'une étude multicentrique impliquant des services d'infectiologie de la région parisienne.

CURSUS ET DIPLOMES UNIVERSITAIRES

1994 Thèse de Biologie médicale, Rennes.

1995 DEA de Biologie Cellulaire et Moléculaire, option Immunologie, Université de Nantes.
Financement FRM.
Laboratoire : ITERT - U 437, Dr. Christine Pourcel.
Criblage d'une banque de cDNA de cellules porcines par le sérum humain total, à la recherche de xénoantigènes impliqués dans le rejet de xénogreffe.

2001 Thèse d' Immunologie, Université Paris VI. Financement CE et CIRMF.
Laboratoires d'accueil : Centre International de Recherches Médicales de Franceville (Gabon) puis Laboratoire de Biologie Parasitaire, Muséum National d'Histoire Naturelle (Paris).
Co-direction : Dr. O. Bain (MNHN) et Pr. P. Debré (CHU Pitié-Salpêtrière).
Etude des mécanismes de protection dans deux modèles de filarioses : *Loa loa* chez des mandrills vaccinés par larves irradiées et *Litomosoides sigmodontis* chez des souris primo-infectées.

mai 2000 – sept 2002 : Post-doc en Parasitologie Biomédicale, P. Druilhe, Institut Pasteur (Paris).
Etude de la réactivité intra-hépatique chez des souris immunisées par des antigènes candidats vaccins de stades hépatiques de *Plasmodium falciparum*.

LANGUES Anglais et Allemand : courants.

AUTRES ACTIVITES Flûte traversière. Dessin. Randonnée.

24.05.05

LISTE DES PUBLICATIONS

1. Analysis of intra-hepatic peptide-specific cell recruitment in mice immunised with *Plasmodium falciparum* antigens.
Hebert A., J-P. Sauzet, M. Lebastard, M-N. Ungeheuer, P. Avé, M. Huerre and P. Druilhe. *J Immunol Methods* 2003, 275 :123-32.

2. Cellular response to *Loa loa* experimental infection in mandrills (*Mandrillus sphinx*) vaccinated with irradiated infective larvae.
M-N. Ungeheuer, N. Elissa, A. Morelli, A. J. Georges, P. Deloron, P. Debré, O. Bain, and P. Millet.
Parasite Immunology 2000, 22 (4) : 173-183.

3. Use of PCR assay for accurate follow-up of *Loa loa* experimental infections in *Mandrillus sphinx*.
F. S. Touré, M-N Ungeheuer, T. G. Egwang, and P. Deloron.
American Journal of Tropical Medicine and Hygiene 1999, 61(6) : 956-959.

4. Drastic reduction of a filarial infection in eosinophilic IL-5 transgenic mice.
C. Martin, L. Le Goff, M-N Ungeheuer, Ph. N. Vuong and O. Bain.
Infect. Immun. 2000, 68 (6) : 3651-3656.

5. Vaccination with irradiated larvae in the filarial model *Litomosoides sigmodontis* – BALB/c mice. Parasite biology and host immune response.
L. Le Goff, C. Martin, I. P. Oswald, Ph. N. Vuong, G. Petit, M-N Ungeheuer and O. Bain.
Parasitology 2000, 120 : 271-280.

6. IL-5 is essential for vaccine-induced protection and for resolution of primary infection in murine filariasis.
C. Martin, K. M. Al-Qaoud, M-N Ungeheuer, K. Paehle, P. N. Vuong, O. Bain, B. Fleischer and A. Hoerauf.
Med. Microb. Immunol. 2000, 189 : 67-74.

7. Resistance and susceptibility to filarial infection with Litomosoides sigmodontis are associated with early differences in parasite development and in localized immune reactions.
Ungeheuer MN, Babayan S, Martin C, Attout T, Belnoue E, Snounou G, Renia L, Korenaga M, Bain O. *Infect Immun.* 2003, 71(12):6820-9.

8. [Bactec 9240 : seeded volume of bottles of blood culture, impact on the results].
J-F Ygout, C. Le Bouquin, M-N Ungeheuer, B. Lanson.
Pathologie Biologie 1996, 44(4): 307-311.

24.05.05